Complete Summary

GUIDELINE TITLE

Pemetrexed for the treatment of malignant pleural mesothelioma.

BIBLIOGRAPHIC SOURCE(S)

National Institute for Health and Clinical Excellence (NICE). Pemetrexed for the treatment of malignant pleural mesothelioma. London (UK): National Institute for Health and Clinical Excellence (NICE); 2008 Jan. 28 p. (Technology appraisal guidance; no. 135).

GUIDELINE STATUS

This is the current release of the guideline.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Malignant pleural mesothelioma (MPM)

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Oncology

INTENDED USERS

Advanced Practice Nurses
Nurses
Pharmacists
Physician Assistants
Physicians

GUIDELINE OBJECTIVE(S)

To evaluate the clinical effectiveness and cost-effectiveness of pemetrexed for the treatment of malignant pleural mesothelioma

TARGET POPULATION

Chemotherapy-naïve patients with malignant pleural mesothelioma in the United Kingdom and Wales who have a World Health Organization (WHO) performance status of 0 or 1, who are considered to have advanced disease and for whom surgical resection is considered inappropriate

INTERVENTIONS AND PRACTICES CONSIDERED

Pemetrexed with cisplatin in selected patients

MAJOR OUTCOMES CONSIDERED

- Prevalence of malignant pleural mesothelioma
- Clinical effectiveness
    - Drug toxicity
    - Symptom palliation
    - Performance status
    - Health-related quality of life
    - Quality-adjusted life years
    - Tumour response rate
    - Overall survival
    - 1-Year survival
    - Median time to progressive disease
- Cost-effectiveness

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Clinical Excellence (NICE) commissioned an independent academic centre to perform a systematic literature review on the technology considered in this appraisal and prepare an assessment report. The assessment report for this technology appraisal was prepared by the Liverpool Reviews and Implementation Group, University of Liverpool (see the "Availability of Companion Documents" field.)

Clinical Effectiveness

Search Strategy

The search incorporated a number of strategies. Search terms for electronic databases included a combination of index terms (e.g., mesothelioma, mesothelial neoplasms and antineoplastic agents) and free text words (e.g., pleural mesothelioma and chemotherapy).

The electronic databases (MEDLINE, EMBASE, Science Citation Index [SCI]/Web of Science, SCI/ISI Proceedings, and the Cochrane Library) were searched for the period from 1980 to May 2005. Search strategies had no language restrictions, and did not include methodological filters that would limit results to specific publication types or study designs. Details of the search strategies used and the number of references retrieved for each search are provided in Appendix 1 of the Assessment Report (see the "Availability of Companion Documents" field).

Reference lists of retrieved articles and pharmaceutical company submissions were searched to identify further studies. Internet resources (including industry supported websites) were examined for information on clinical trials. In addition, handsearching of the American Society of Clinical Oncology (ASCO) conference proceedings (2003 to 2005) was conducted.

An advisory panel was established to guide the review process. The role of the advisory panel was to comment on the review protocol, to answer specific questions as the review progressed and to comment on an early draft of the review including the identification of missed or ongoing studies.

Inclusion and Exclusion Criteria

The identified citations were assessed for inclusion through two stages and disagreements were resolved by discussion at each stage. Two reviewers independently scanned all the titles and abstracts and identified the potentially relevant articles to be retrieved. Full text copies of the selected papers were obtained and each assessed by two reviewers for inclusion.

Study Design

- Randomised controlled trial (RCT)
- Non-RCT (e.g., non randomised phase I, phase II trials)

Patient Population

Chemotherapy-naïve patients with unresectable malignant pleural mesothelioma

Interventions

Pemetrexed disodium (Alimta, LY231514, MTA) and cisplatin in combination, supplemented by folic acid and vitamin B12

Comparators

- Cisplatin
- Supportive care
- Other commonly used alternatives (e.g., vinorelbine, or MVP [mitomycin C, vinblastine, and cisplatin])

Outcomes

- Overall survival
- Toxicity
- Symptom palliation
- Health-related quality of life
- Tumour response
- Progression-free survival

Exclusion Criteria

Study populations other than those described above

Cost-Effectiveness

Search Strategy

A comprehensive review of the literature was undertaken to identify all published articles that could provide evidence with regard to the cost-effectiveness of pemetrexed plus cisplatin for the treatment of malignant pleural mesothelioma. This was carried out in conjunction with the search strategy for clinical effectiveness studies.

The reviewers undertaking the review of clinical effectiveness made note of the papers which appeared to contain economic or cost evidence and made this available to the economic reviewers. Reference lists of retrieved articles and pharmaceutical company submissions were also searched to identify further studies.

Inclusion and Exclusion Criteria

The aim of the economic review was to identify economic evaluations informed by clinical data from randomised and/or non-randomised controlled trials. After scanning the abstracts, all papers that appeared to be of potential value to the study were obtained. Using explicit, predetermined criteria, two reviewers independently identified studies for inclusion in the cost-effectiveness review process. Disagreements were resolved through discussion.

Refer to Table 3A of the Assessment Report (see the "Availability of Companion Documents" field) for details regarding databases searched and inclusion and exclusion criteria used.

NUMBER OF SOURCE DOCUMENTS

Clinical Effectiveness

- One randomised controlled trial (RCT) comparing pemetrexed plus cisplatin with cisplatin alone met the inclusion criteria.
- Eli Lilly and Company Limited provided a full trial report.

Cost-Effectiveness

- One conference abstract/presentation
- An economic submission from the manufacturer

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Clinical Excellence (NICE) commissioned an independent academic centre to perform a systematic literature review on the technology considered in this appraisal and prepare an assessment report. The assessment report for this technology appraisal was prepared by the Liverpool Reviews and Implementation Group, University of Liverpool (see the "Availability of Companion Documents" field.)

Clinical Effectiveness

Data Extraction

Data extraction was carried out by two reviewers. Individual study data relating to study design and findings were extracted independently by one reviewer into a predesigned data extraction form and checked by a second reviewer.

Quality Assessment

Two reviewers independently evaluated the included studies for methodological quality. This involved methodological assessment for clinical effectiveness based on Centre for Reviews and Dissemination, York, Report 4 (see Appendix 2 of the Assessment Report [see the "Availability of Companion Documents" field]). Any discrepancies were resolved through discussion.

Methods of Analysis/Synthesis

Individual study data and quality assessment were summarised in structured tables and as a narrative description. Results from non-randomised controlled trials were tabulated and presented narratively.

For binary outcomes, relative treatment effects were presented in the form of relative risks (RR) with 95% confidence intervals.

Cost-Effectiveness

All cost-effectiveness data were abstracted by a single reviewer and then checked by a second reviewer.

Quality Assessment

Cost-effectiveness studies were quality assessed by two reviewers using criteria updated from the checklist developed by Drummond and Jefferson (see Appendix 2 of the Assessment Report [see the "Availability of Companion Documents" field]).

Methods of Analysis for Economic Studies

Individual study data and quality assessment were presented in structured tables and as a narrative description.

To supplement findings from the economic literature review, additional cost and benefit information from other sources, including the industry submissions to National Institute for Health and Clinical Excellence (NICE), were collated and presented as appropriate.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Considerations

Technology appraisal recommendations are based on a review of clinical and economic evidence.

Technology Appraisal Process

The National Institute for Health and Clinical Excellence (NICE) invites 'consultee' and 'commentator' organisations to take part in the appraisal process. Consultee organisations include national groups representing patients and carers, the bodies representing health professionals, and the manufacturers of the technology under review. Consultees are invited to submit evidence during the appraisal and to comment on the appraisal documents.

Commentator organisations include manufacturers of the products with which the technology is being compared, the National Health Service (NHS) Quality Improvement Scotland and research groups working in the area. They can comment on the evidence and other documents but are not asked to submit evidence themselves.

NICE then commissions an independent academic centre to review published evidence on the technology and prepare an 'assessment report'. Consultees and commentators are invited to comment on the report. The assessment report and the comments on it are then drawn together in a document called the evaluation report.

An independent Appraisal Committee then considers the evaluation report. It holds a meeting where it hears direct, spoken evidence from nominated clinical experts, patients and carers. The Committee uses all the evidence to make its first recommendations, in a document called the 'appraisal consultation document' (ACD). NICE sends all the consultees and commentators a copy of this document and posts it on the NICE website. Further comments are invited from everyone taking part.

When the Committee meets again it considers any comments submitted on the ACD; then it prepares its final recommendations in a document called the 'final appraisal determination' (FAD). This is submitted to NICE for approval.

Consultees have a chance to appeal against the final recommendations in the FAD. If there are no appeals, the final recommendations become the basis of the guidance that NICE issues.

Who is on the Appraisal Committee?

NICE technology appraisal recommendations are prepared by an independent committee. This includes health professionals working in the NHS and people who are familiar with the issues affecting patients and carers. Although the Appraisal Committee seeks the views of organisations representing health professionals, patients, carers, manufacturers and government, its advice is independent of any vested interests.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

Estimates of cost effectiveness were provided by the manufacturer and by the Assessment Group. A review of the published literature identified a single cost-effectiveness study. This was a conference presentation/abstract that was a forerunner of the manufacturer's submission.

Two cost-effectiveness models were submitted by the manufacturer. Model 1 compared pemetrexed plus cisplatin with cisplatin alone. Model 2 compared pemetrexed plus cisplatin with standard care (as defined by the manufacturer on the basis of a market research survey). Both models had a 29-month time horizon (reflecting the trial follow-up period) and took a health service perspective. Both considered outcomes in terms of life years gained and quality-adjusted life years (QALYs). No discounting was applied to costs, because they were all incurred within 1 year. Outcomes were discounted at 3.5%.

The economic analyses carried out by the manufacturer and the Assessment Group, using model 1, both indicated an incremental cost per QALY gained of greater than 60,000 pounds when pemetrexed plus cisplatin was compared with cisplatin alone in the fully supplemented population. Pemetrexed plus cisplatin, when compared with cisplatin alone, appears to have lower incremental cost-effectiveness ratios (ICERs) in patients with advanced disease and/or good performance status. The manufacturer's economic analyses (based on indirect comparisons) using model 2 indicated more favourable ICERs for pemetrexed plus cisplatin when compared with MVP, vinorelbine, and ASC. However, the assumptions underpinning model 2 are subject to high levels of uncertainty. When the assumptions were modified to reflect performance-status-adjusted survival, and resource use based on published data, the ICERs from model 2 were in line with those of pemetrexed plus cisplatin versus cisplatin alone.

See Sections 4.2.2 through 4.2.9 of the original guideline document for a detailed description of the two economic models examined.

METHOD OF GUIDELINE VALIDATION

External Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Consultee organizations from the following groups were invited to comment on the draft scope, Assessment Report and the Appraisal Consultation Document (ACD) and were provided with the opportunity to appeal against the Final Appraisal Determination.

- Manufacturer/sponsors
- Professional/specialist and patient/carer groups
- Commentator organisations (without the right of appeal)

In addition, individuals selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups were also invited to comment on the ACD.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Pemetrexed is recommended as a treatment option for malignant pleural mesothelioma only in people who have a World Health Organization (WHO) performance status of 0 or 1, who are considered to have advanced disease and for whom surgical resection is considered inappropriate.

Patients currently receiving pemetrexed who do not fall into the patient population defined above should have the option to continue therapy until they and their clinicians consider it appropriate to stop.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of evidence supporting the recommendations is not specifically stated.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Appropriate use of pemetrexed for the treatment of malignant pleural mesothelioma
- Improvement in symptoms (dyspnea, pain) and maintenance of quality of life for as long as possible

POTENTIAL HARMS

- Severe to life-threatening or disabling adverse events were statistically significantly more frequent in patients receiving pemetrexed plus cisplatin than in those receiving cisplatin alone. The most commonly reported of these in patients receiving pemetrexed plus cisplatin were: neutropenia (27.9%), leukopenia (17.7%), nausea (14.6%) and vomiting (13.3%). Supplementation with folic acid and vitamin B12 resulted in a consistent reduction in the severity and incidence of adverse events (except for dehydration) in the pemetrexed plus cisplatin arm. The most common severe adverse events in fully supplemented patients randomised to pemetrexed plus cisplatin were: neutropenia (23.2%), leukopenia (14.9%), nausea (11.9%) and vomiting (10.7%).
- Adverse effects commonly associated with pemetrexed include nausea, vomiting, fatigue and neutropenia. Skin rash, mucositis and liver function abnormalities have also been reported. Cisplatin causes nausea and vomiting in the majority of patients. This is controllable in 50% to 80% of patients with anti-emetic drugs. Serious toxic effects of cisplatin on the kidneys, bone

marrow and ears are common, and serum electrolyte disturbances, hyperuricaemia, allergic reactions and cardiac abnormalities have also been reported.

For full details of side effects and contraindications, see the summaries of product characteristics http://emc.medicines.org.uk/.

CONTRAINDICATIONS

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For full details of contraindications, see the summaries of product characteristics at http://emc.medicines.org.uk/.

QUALIFYING STATEMENTS

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This guidance represents the view of the Institute, which was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. The guidance does not, however, override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

- The Healthcare Commission assesses the performance of National Health Service (NHS) organizations in meeting core and developmental standards set by the Department of Health in "Standards for better health" issued in July 2004. The Secretary of State has directed that the NHS provides funding and resources for medicines and treatments that have been recommended by the National Institute for Health and Clinical Excellence (NICE) technology appraisals normally within 3 months from the date that NICE publishes the guidance. Core standard C5 states that healthcare organisations should ensure they conform to NICE technology appraisals.
- "Healthcare Standards for Wales" was issued by the Welsh Assembly Government in May 2005 and provides a framework both for self-assessment by healthcare organisations and for external review and investigation by Healthcare Inspectorate Wales. Standard 12a requires healthcare organisations to ensure that patients and service users are provided with effective treatment and care that conforms to NICE technology appraisal guidance. The Assembly Minister for Health and Social Services issued a Direction in October 2003 which requires Local Health Boards and NHS Trusts to make funding available to enable the implementation of NICE technology appraisal guidance, normally within 3 months.
- NICE has developed tools to help organisations implement this guidance (listed below). These are available on the NICE website

(http://guidance.nice.org.uk/TA135 [see also the "Availability of Companion Documents" field]).

- A costing statement explaining the resource impact of this guidance
- Audit criteria to monitor local practice

IMPLEMENTATION TOOLS

Audit Criteria/Indicators
Patient Resources
Quick Reference Guides/Physician Guides
Resources

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

End of Life Care
Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

National Institute for Health and Clinical Excellence (NICE). Pemetrexed for the treatment of malignant pleural mesothelioma. London (UK): National Institute for Health and Clinical Excellence (NICE); 2008 Jan. 28 p. (Technology appraisal guidance; no. 135).

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2008 Jan

GUIDELINE DEVELOPER(S)

National Institute for Health and Clinical Excellence (NICE) - National Government Agency [Non-U.S.]

SOURCE(S) OF FUNDING

National Institute for Health and Clinical Excellence (NICE)

GUIDELINE COMMITTEE

Appraisal Committee

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Committee Members: Professor Keith Abrams, Professor of Medical Statistics, University of Leicester; Dr Jeff Aronson, Reader in Clinical Pharmacology, Radcliffe Infirmary, Oxford; Dr Darren Ashcroft, Senior Clinical Lecturer, School of Pharmacy and Pharmaceutical Sciences, University of Manchester; Professor David Barnett, Professor of Clinical Pharmacology, University of Leicester; Dr Peter Barry, Consultant in Paediatric Intensive Care, Leicester Royal Infirmary; Professor Stirling Bryan, Director of the Health Economics Facility, University of Birmingham; Mr Brian Buckley, Vice Chairman, InContact; Professor John Cairns, Public Health and Policy, London School of Hygiene and Tropical Medicine; Professor Mike Campbell, Statistician, University of Sheffield; Professor David Chadwick, Professor of Neurology, Walton Centre for Neurology and Neurosurgery; Dr Mark Chakravarty, Head of Government Affairs and NHS Policy, Procter and Gamble Pharmaceuticals (UK) Ltd; Dr Peter I Clark, Honorary Chairman, Association of Cancer Physicians; Dr Mike Davies, Consultant Physician, University Department of Medicine & Metabolism, Manchester Royal Infirmary; Mr Richard Devereaux-Phillips, Public Affairs Manager, Medtronic Ltd; Professor Jack Dowie, Health Economist, London School of Hygiene and Tropical Medicine; Lynn Field, Nurse Director, Pan Birmingham Cancer Network; Professor Christopher Fowler, Professor of Surgical Education, University of London; Dr Fergus Gleeson, Consultant Radiologist, Churchill Hospital, Oxford; Ms Sally Gooch, Former Director of Nursing & Workforce Development, Mid Essex Hospitals Services NHS Trust; Mrs Barbara Greggains, Lay Member; Mr Sanjay Gupta, Former Stroke Services Manager, Basildon and Thurrock Universities Hospitals NHS Trust; Professor Philip Home, Professor of Diabetes Medicine, University of Newcastle upon Tyne; Dr Peter Jackson, Clinical Pharmacologist, University of Sheffield; Professor Peter Jones, Professor of Statistics & Dean Faculty of Natural Sciences, Keele University; Dr Mike Laker, Medical Director, Newcastle Hospitals NHS Trust; Dr George Levvy, Lay Member; Ms Rachel Lewis, Nurse Adviser to the Department of Health; Mr Terence Lewis, Mental Health Consultant, National Institute for Mental Health in England; Professor Jonathan Michaels, Professor of Vascular Surgery, University of Sheffield; Professor Gary McVeigh, Professor of Cardiovascular Medicine, Queen's University, Belfast; Dr Ruairidh Milne, Senior Lecturer in Health Technology Assessment, National Coordinating Centre for Health Technology; Dr Neil Milner, General Medical Practitioner, Tramways Medical Centre, Sheffield; Dr Rubin Minhas, General Practitioner, CHD Clinical Lead, Medway PCT; Dr John Pounsford, Consultant Physician, North Bristol NHS Trust; Dr Rosalind Ramsay, Consultant Psychiatrist, Adult Mental Health Services, Maudsley Hospital; Dr Stephen Saltissi, Consultant Cardiologist, Royal Liverpool University Hospital; Dr Lindsay Smith, General Practitioner, East Somerset Research Consortium; Mr Cliff Snelling, Lay Member; Mr Miles Scott, Chief Executive, Bradford Teaching Hospitals NHS Foundation Trust; Dr Ken Stein, Senior Lecturer, Peninsula Technology Assessment Group (PenTAG), University of

Exeter; Professor Andrew Stevens, Professor of Public Health, University of Birmingham

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) format from the National Institute for Health and Clinical Excellence (NICE) Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Pemetrexed for the treatment of malignant pleural mesothelioma. Quick reference guide. London (UK): National Institute for Health and Clinical Excellence (NICE); 2008 Jan. 2 p. (Technology appraisal 135). Available in Portable Document Format (PDF) from the National Institute for Health and Clinical Excellence (NICE) Web site.
- Pemetrexed for the treatment of malignant pleural mesothelioma. Costing statement. London (UK): National Institute for Health and Clinical Excellence (NICE); 2008 Jan. 2 p. (Technology appraisal 135). Available in Portable Document Format (PDF) from the NICE Web site.
- Pemetrexed for the treatment of malignant pleural mesothelioma. Audit support. London (UK): National Institute for Health and Clinical Excellence (NICE); 2008. 6 p. (Technology appraisal 135). Available in Portable Document Format (PDF) from the NICE Web site.
- Pemetrexed disodium for the treatment of malignant pleural mesothelioma: a systematic review and economic evaluation. Assessment report. London (UK): National Institute for Health and Clinical Excellence (NICE); 2006 Mar 31. 105 p. (Technology appraisal 135). Available in Portable Document Format (PDF) from the NICE Web site.

Print copies: Available from the National Health Service (NHS) Response Line 0870 1555 455. ref: N1454. 11 Strand, London, WC2N 5HR.

PATIENT RESOURCES

The following is available:

- Pemetrexed for malignant pleural mesothelioma. Understanding NICE guidance - Information for people who use NHS services. London (UK):

National Institute for Health and Clinical Excellence (NICE); 2008 Jan. 4 p. (Technology appraisal 135).

Electronic copies: Available in Portable Document Format (PDF) from the National Institute for Health and Clinical Excellence (NICE) Web site.

Print copies: Available from the NHS Response Line 0870 1555 455. ref: N1455. 11 Strand, London, WC2N 5HR.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC STATUS

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